

Cancer Genomic Instability

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CANCER
RESEARCH
UK

LUNG CANCER
CENTRE OF
EXCELLENCE



FDA Approvals 2002-2014

- 71 anticancer drugs approved including 52 Targeted/Precision medicines
- 23 drugs : only progression free survival data provided: no OS
- Median improvement in Overall Survival 2.1 months
- **Mismatch between cost and benefit**
- Costs of cancer drugs doubled in 10 years- now \$10,000 per month
- Cost per life year saved \$2.7 million (Kantarjian JCO 2013)
- In 2012 12 drugs approved-
 - 11 priced >\$100,000 for an average course
 - Only 3 improved Overall survival, 2 by less than 2 months

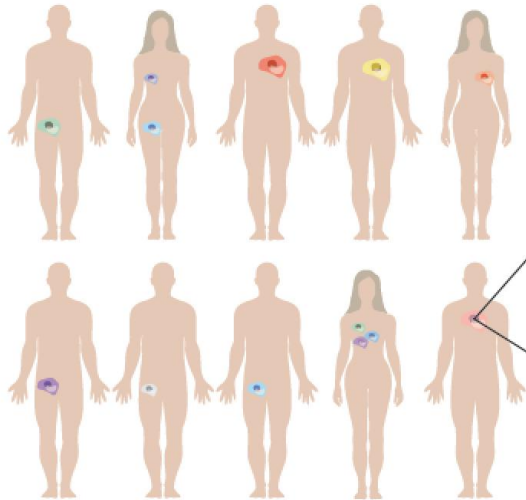
Current precision cancer medicine strategies are not sustainable

Precision medicine strategies are not improving outcomes commensurate with price

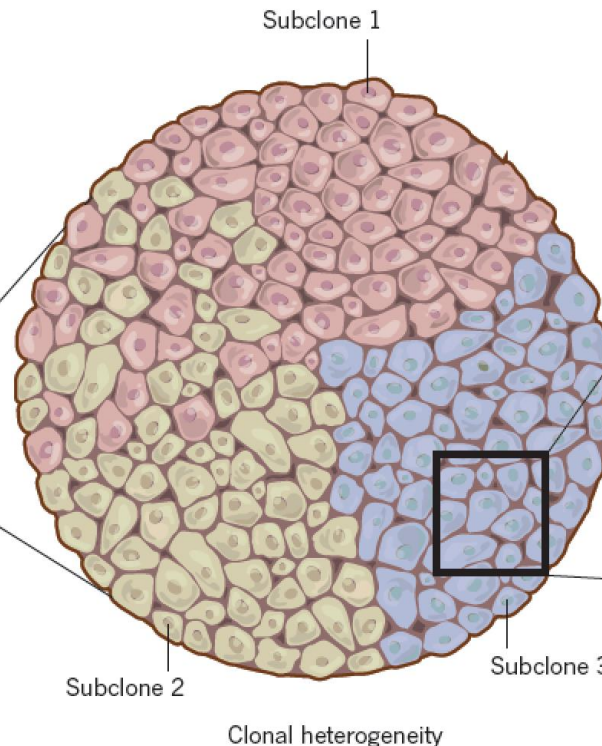
Why is this so challenging?

Implications for Therapy and Outcome

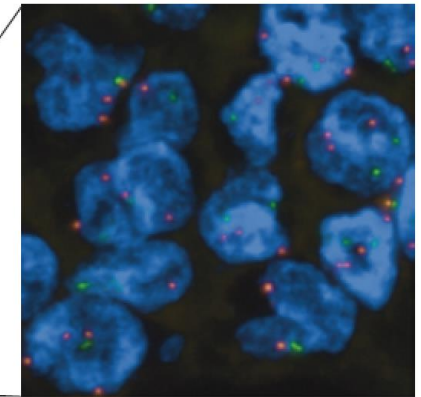
Intertumour Heterogeneity



Intratumour Heterogeneity



Intercellular Heterogeneity

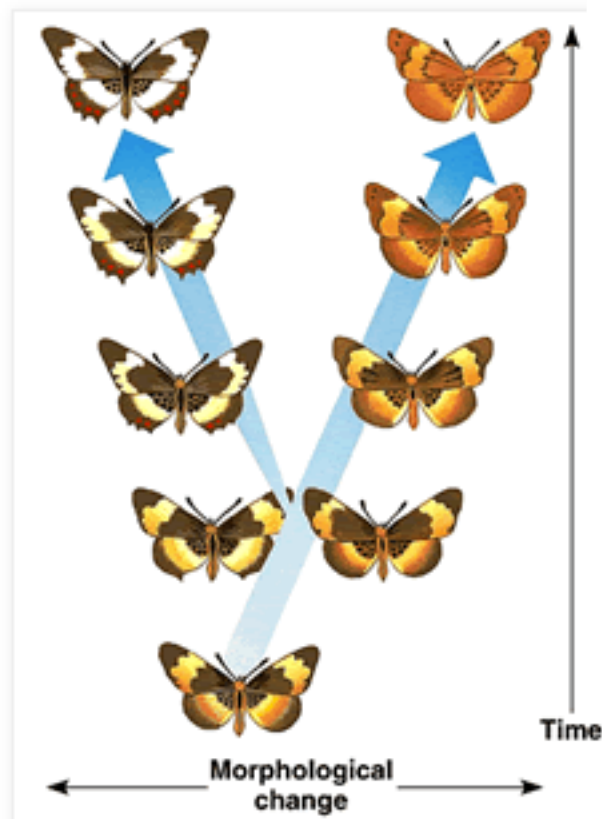


Intercellular genetic and non-genetic heterogeneity


- Achieving cures in metastatic disease
- Cost of cancer drug development :Stable vs Unstable genomes
- Cancer biomarker validation

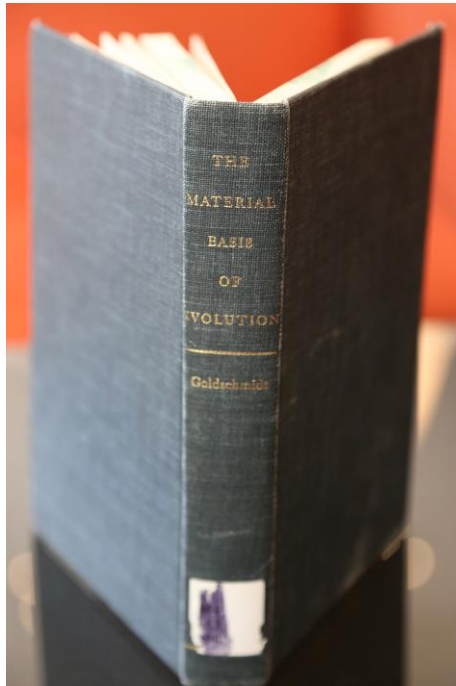
Microevolution: Gradualism

- Darwin argued that nature never makes jumps : *natura non facit saltum*
- Profound change is the result of a slow but continuous processes
- Gradual accumulation of small mutations as drivers of change (Neo-Darwinism)



Macroevolution: “Hopeful Monsters”

- Goldschmidt argued that large changes in evolution were caused by “macromutations”
- Chromosomal rearrangements result in **Macroevolutionary leaps**  **Speciation**
- **Rare events resulting in profound change: “Hopeful monsters”**



Macroevolution and Hopeful Monsters

“**macroevolution** must proceed by a different genetic method.... Only the **arrangement of the serial chemical constituents of the chromosome into a new, spatially different order**; ie. A new chromosomal pattern, is involved”.

Goldschmidt “Material Basis of Evolution” 1960

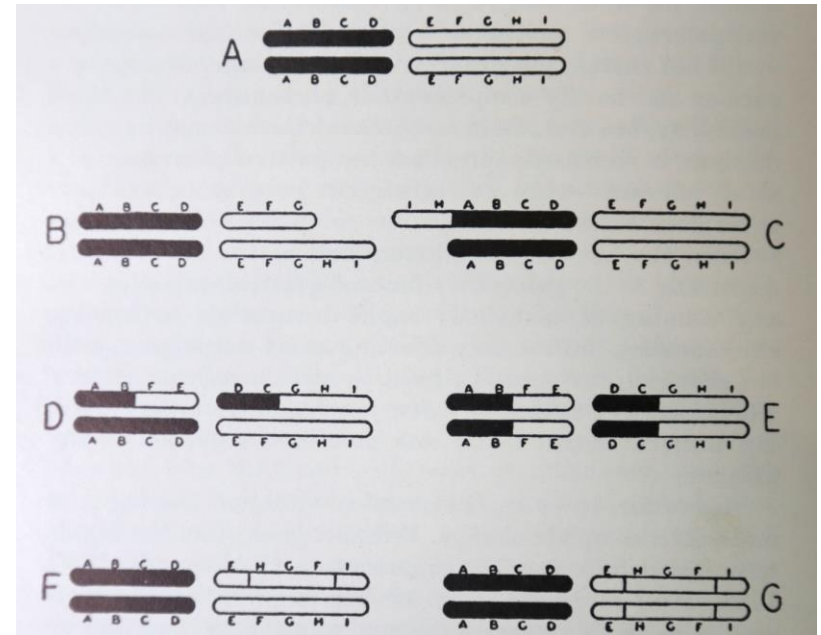
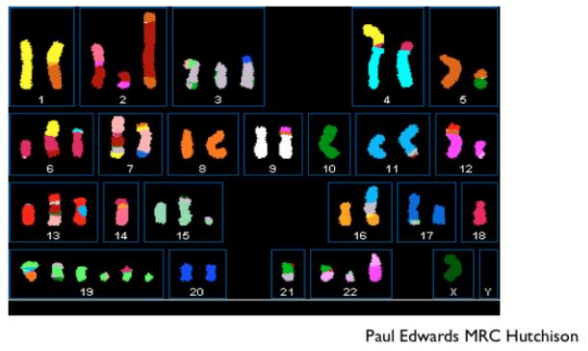


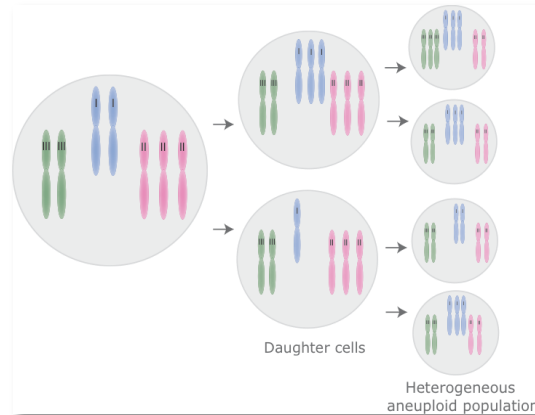
Fig 35 Simple types of chromosomal rearrangements

Patterns of Cancer Chromosomal Rearrangements

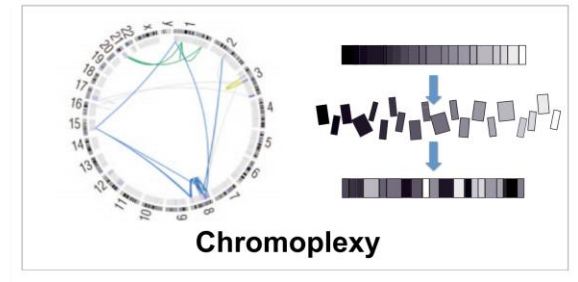
Structural CIN



Numerical CIN

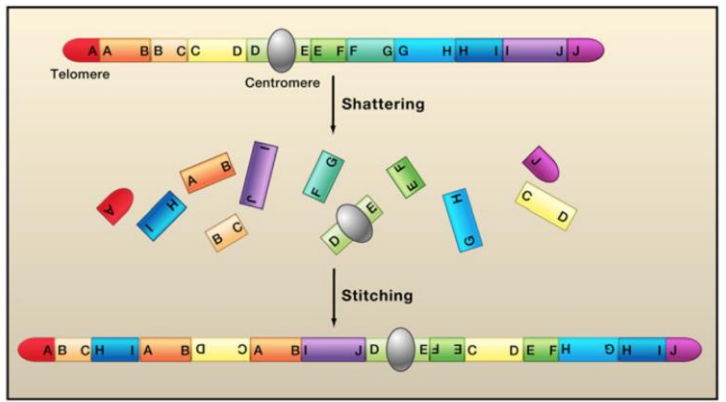


Chromoplexy (Garraway)

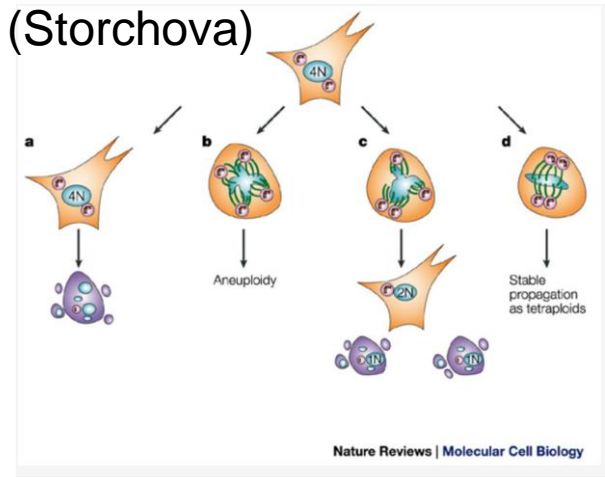


Chromothripsis (Campbell/Meyerson)

Single chromosome fragmented and reassembled



Genome Doubling (Storchova)

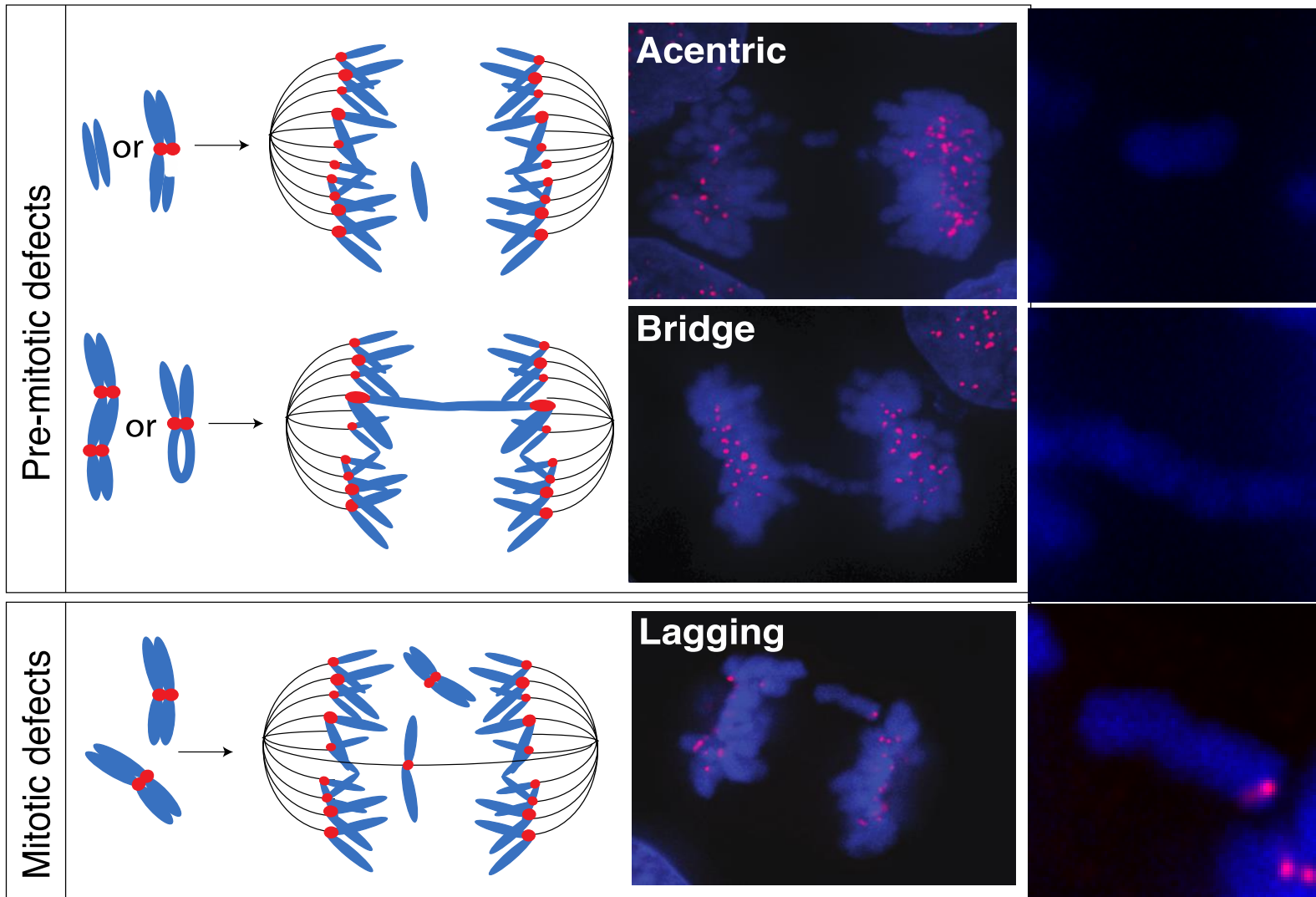


Generates Profound Cell-to-Cell heterogeneity: fuel for phenotypic change (Pavelka Nature 2010)

Chromosome segregation errors and CIN

Chromosome fragments with no centromere and anaphase bridges: Structural aberrations resulting from pre-mitotic defects

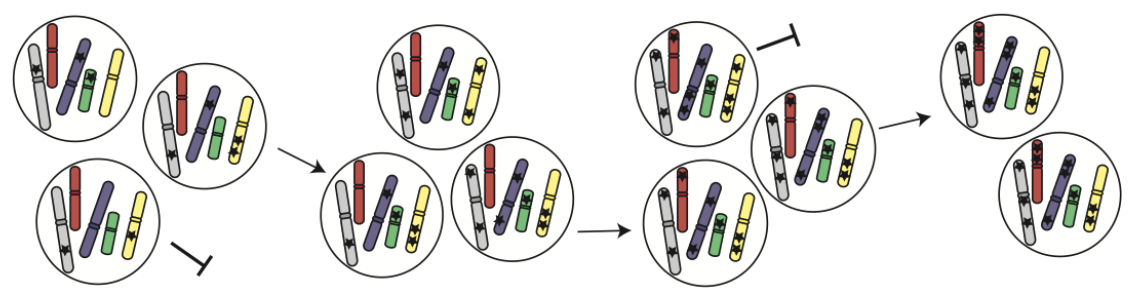
DAPI ACA



Lagging Chromosome with Centromere: Improper attachments Mitotic Dysfunction

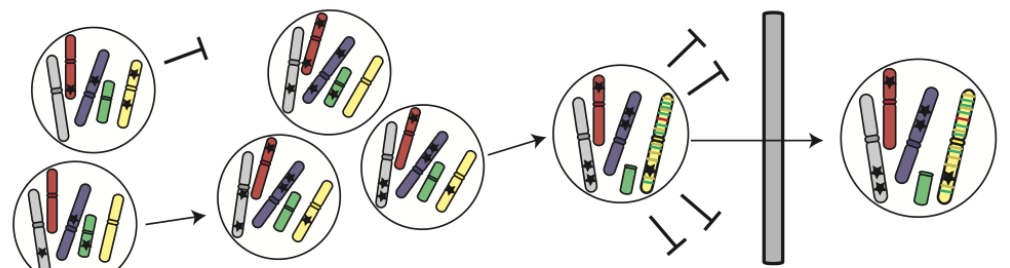
Gisselsson (2008)

DNA repair



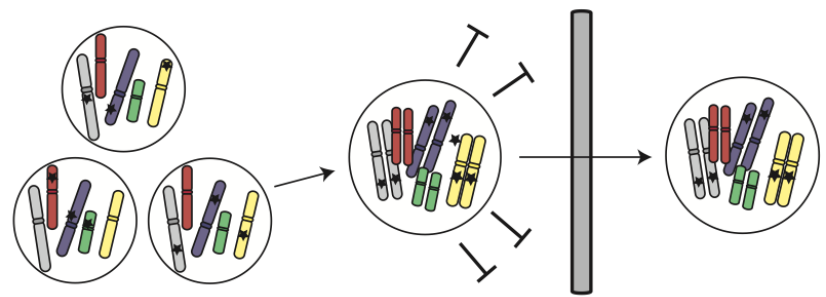
- acquisition of combination of mutations needed to cross selection barrier

CIN



- catastrophic chromosome rearrangement

Genome Doubling



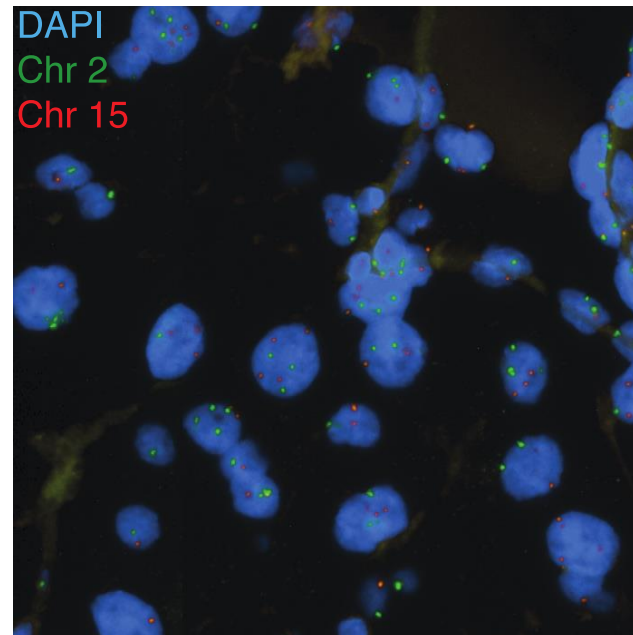
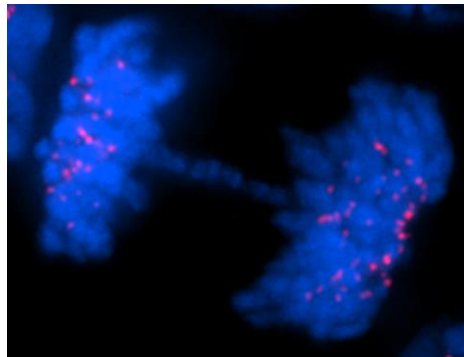
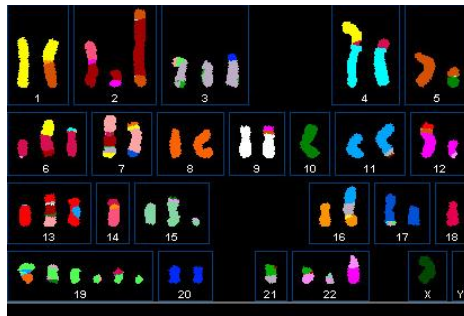
- whole genome doubling

Relative evolutionary time

★ Mutation → Survival of clone ┐ Extinction of clone

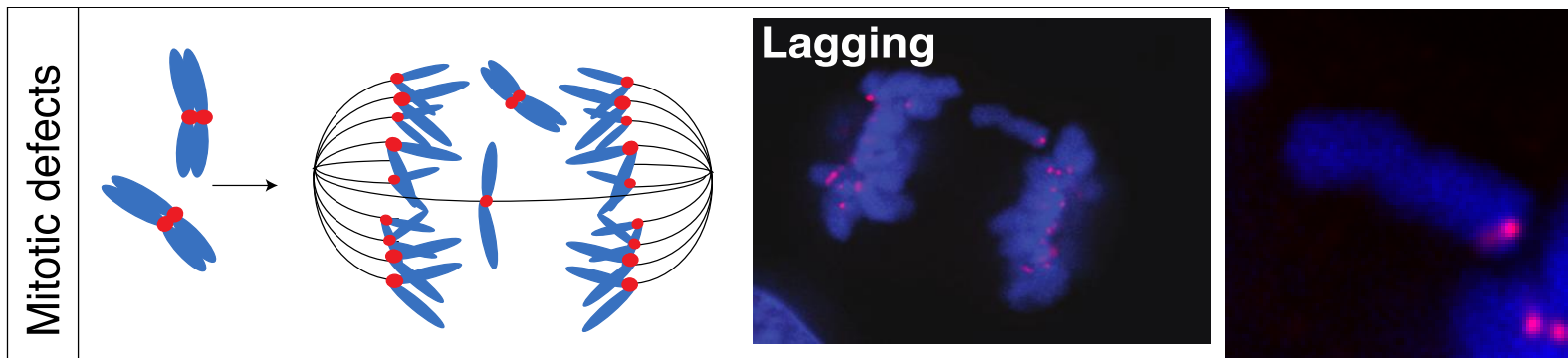
Mechanisms of Chromosomal Instability

- CIN can be structural and numerical: commonly occur together
- Increasing understanding of how these two patterns of diversity may be linked- **Medema, Burrell, Bartek**
- Aneuploidy common feature of solid tumours- Targeting Aneuploidy- **Tak Mak**



Chromosome segregation errors and CIN

Rene Medema Mitotic Aberrations Generating Numerical and Structural CIN

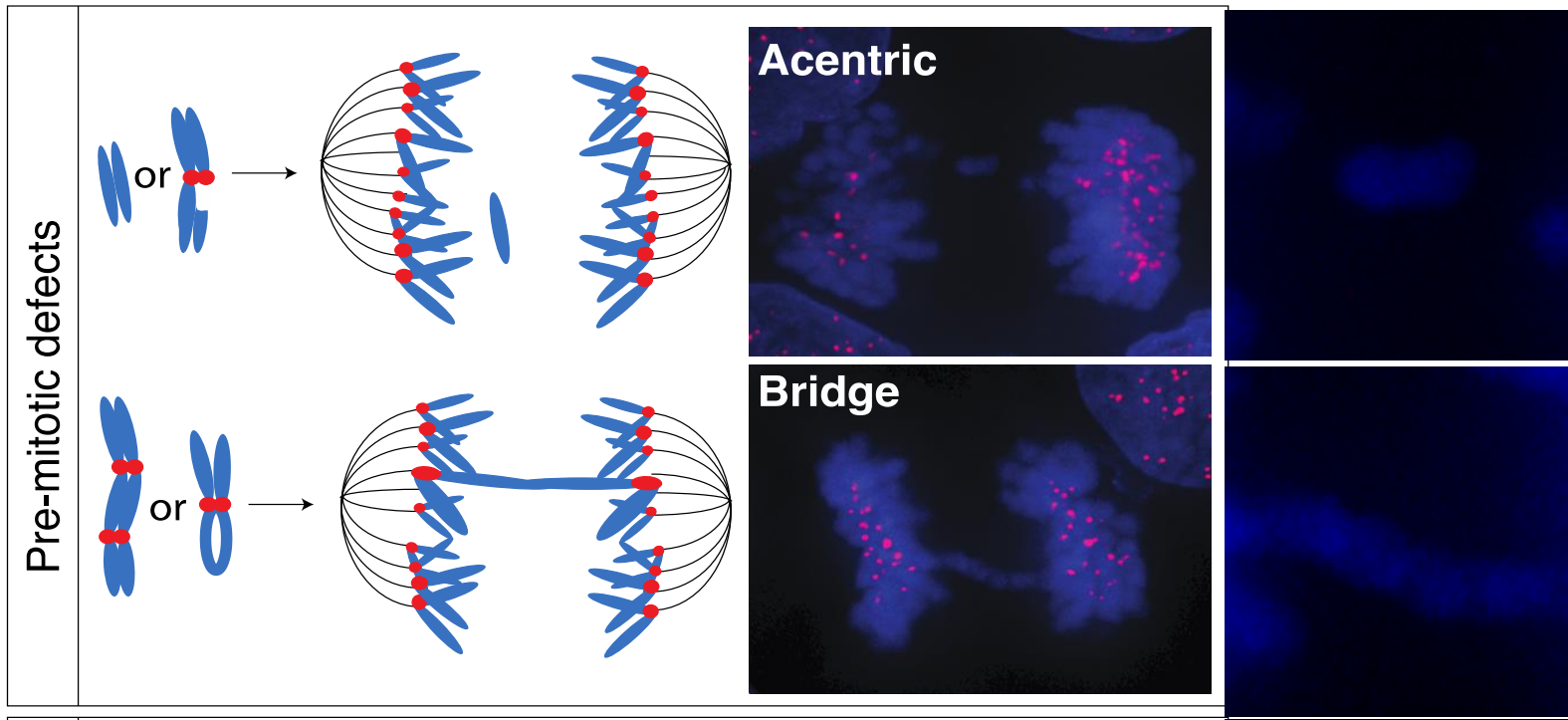


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Chromosome segregation errors and CIN

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DAPI ACA



Burrell and Bartek

How DNA replication errors before Mitosis trigger diversity

Tak Mak

Targeting Aneuploidy